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EXAMINER	
HAYES, R	
ART UNIT	PAPER NUMBER
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DATE MAILED: 03/04/97

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 11/27/96 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 12-25 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 12-25 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

DETAILED ACTION

Response to Amendment

1. The amendment filed 11/27/96 has been entered.

2. The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1818.

3. The rejection of claims 12-25 under 35 U.S.C. § 112, first paragraph, as it relates to the issue of an enabling disclosure of "neurotrophic fragments", is withdrawn due to the amendment of the claim.

4. The rejection of claims 18 under 35 U.S.C. § 112, second paragraph is withdrawn due to the amendment of the claim.

5. Applicant's arguments filed 11/27/96 have been fully considered but they are not deemed to be persuasive.

6. The disclosure is objected to because of the following informalities: Claim 22 now recites "[a] method for *of treating*..." . Appropriate correction is required.

7. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

8. The Declaration under 37 CFR 1.132 filed 11/27/96 is insufficient to overcome the rejection of claims 12-25 that is based upon the lack of an enabling disclosure under 35 U.S.C. 112, first paragraph, because the Declaration does not address those issues germane to the rejection made of record. The Declaration states in paragraph 5 that "[t]he cell population of explants comprises a heterogenous cell environment that mimics the *in vivo* environment. Thus, it is predictive of *in vivo* results." However, "a heterogenous cell environment" does not mimic the *in* vivo environment in regards to maintaining neural pathways (e.g., including the cerebellar pathways of the explant versus any other neural pathways encompassed by the claims that include those disease states recited in claims 14 & 25), or as they relate to issues of damaged neural processes (i.e., resulting from obtaining the explant itself) that result in eventual cell death. The Declaration then states in *pp* 13 that "[t]he methods of the present invention appear to protect vulnerable neurons around the site of injury which would otherwise degenerate", etc. However, this is not persuasive, because without sufficient neural structure, there is no possible maintenance of function. Moreover, in both instances no documentary evidence is presented to support this opinion; nor that directly addresses the issues raised in the *prima facie* case of nonenablement set forth in the previous Office action; nor any documentary evidence demonstrating that those methods disclosed in the specification were utilized for the *in vivo* administration of prosaposin

for "treating [any] demyelination disorder in a mammal", for "preventing or slowing the progress of neural or myelin degeneration in neural tissue [*in vivo*]", or for "treating neuronal degeneration in the central or peripheral nervous system ... in a mammal", as claimed. The cells of the *ex vivo* explant still eventually die; therefore, no "prevention" of degeneration or demyelination, for example, is apparent.

The issue then becomes two-fold. The *in vitro* results of Exhibits A & B provide no nexus to *in vivo* administration or "effective treatment"(as it relates to *pp* 6 of the Declaration), and that the method steps, animal models and assays to determine "effective treatment" as provided in the Declaration (i.e., Exhibits C, D, E, G, H or J) were not disclosed in the specification, nor can they be extrapolated from the single *ex vivo* model disclosed in the specification. In other words, enablement must be established in the specification at the time of filing and is to be commensurate in scope with the stated claims. *In re* Hogan and Banks, 194 USPQ 527 (1977).

The Declaration states in *pp* 6 that "prevention of cell death (demyelination) in immortalized Schwann cell in culture (Exhibit A)" is shown. However, cell death in culture is not equivalent to demyelination *in vivo*, nor are Schwann cells representative of demyelination events within the CNS (i.e., where oligodendrocytes are the cell type responsible for myelination; as it also relates to the comments in *pp* 13 of the Declaration). Exhibit B shows only incorporation of S35 into sulfolipids of cultured Schwann cells. Incorporation of S35 into sulfolipids of cultured Schwann cells is not equivalent to administration of prosaposin to a mammal, nor to CNS demyelination disorders, nor addresses issues related to neuronal degeneration, as claimed.

Exhibit C demonstrates a mutant mouse model in which sphingolipid activator protein precursor is inactivated. It is noted that this model was not developed until 3 years after the priority date of the instant application, and thus provides further evidence that a significant amount of experimentation was required in order to even discover a model system to assess enablement of some of the different aspects of Applicants' invention. It is also noted that no administration of prosaposin to this animal was described in this reference.

Exhibit D nor E demonstrate "preventing... the progress of neural or myelin degeneration". However, Figure 2 (Exhibit D) still shows decreased neuron density at 7 day postlesion, as does Figure 4B (Exhibit E); thereby, providing evidence that "neural degeneration" can not be "prevented"; in contrast to the assertions made in paragraph 13 of the Declaration. In that these neurons and oligodendrocytes still die, vulnerable neurons around the site of injury which otherwise degenerate, still degenerate. Moreover, increased cell survival or neurite outgrowth is not equivalent to "slowing/halting" or "effectively treating" neuronal degeneration, which requires functional synaptogenesis to prevent eventual cell death, which the Declaration appears to acknowledge in *pp* 13. It is not clear, however, that the "invention clearly retards or halts the degeneration *of at least some injured* myelinated axons" (*pp* 13, last sentence), because it is not known what specific neurons or myelinated cells these were. The ischemic models of Exhibits D or E are also not representative of any other degenerative events except stoke (as recited in claim 25), nor is it necessarily representative of demyelination events (as it relates to claims 12-17). In addition, the behavior assays described in these publications were not disclosed

in the instant specification, nor can they be extrapolated from the specification.

Although Exhibit F demonstrates "neural outgrowth" of about 10 millimeters (i.e., in a non-inhibiting environment for neurite outgrowth; therefore, not representative of the CNS), this provides no nexus for "treating, slowing or preventing" neurodegeneration, because without functional synaptogenesis these neurons still die. Further, Exhibit F discloses that "it remains to be determined what types of neurons, other than substance P-containing neurons, are supported by prosaposin" (pg. 2024, 2nd *pp*). Thus, it is not known if any neural or demyelinating disorder can be "treated" that does not involve substance P-containing *peripheral* neuronal cell populations in order to even begin to carry out the instant invention (i.e., based on art 3 years after the priority date of the instant application).

Exhibit G describes administration of a saposin C-derived peptide to diabetic rats, while Exhibit H shows the results of administration to taxol-treated animals. In neither case is it apparent that neuronal degeneration or demyelination is "prevented, slowed or effectively treated". Further, it is unknown what the significance of the results are in Exhibit H, in which most of time points overlap with control values. Additionally, both exhibits appear to only attempt to address peripheral neuropathy versus the CNS components encompassed by the claims (e.g., as it relates to claims 14-15, 23-25). Exhibit I then describes motor and sensory conductance velocities in diabetic rats following treatment with saposin C-derived peptide. Again, it is unknown whether peripheral neuronal degeneration or peripheral demyelination is "prevented, slowed or effectively treated". It is noted that none of the data points return to

control values. Thus, no "prevention" is evident. The same arguments appear to apply to the Chung rat model of Exhibit J. However, it is not clear how an allodynic state relates to prevention of peripheral neuropathy, or demyelination as claimed, in which motor neural degeneration or sensory degeneration could also increase the threshold presure tolerated by these rats (i.e., degeneration which results in a more non-responsive phenotype), when no control values are displayed, nor data related to different days postlesion are provided.

The Declaration raises as its final issue that IGF-1 "significantly reduced the number and areas of demyelinating lesions *in vivo*." However, the issue remains that IGF is not representative of prosaposin, nor that the methods steps or the animal model presented in Exhibit K were disclosed in the specification, nor that they can be extrapolated from the single *ex vivo* model disclosed in the specification. It is well known in the art that an IGF transporter protein exists that allows administration of IGF across the blood brain barrier, in contrast to other putative neurotrophic factors. However, passage of IGF-1 across the BBB is not the sole issue germane to "effective treatment" of any neurological or demyelinating disorder. It merely demonstrates one component in a cascade of problems in this unpredictable art, which are of record, and which prevents the skilled artisan from knowing how to make the instant invention work. In other words, the mere correlation between *in vitro* and *in vivo* activity of neurotrophic factors addresses none of the issues made of record.

In summary, the neurite outgrowth demonstrated in the single example of *ex vivo* mouse cerebellar explants, or increased cell survival demonstrated by *in vitro* cell culture disclosed in the

instant invention, provides no nexus for the breadth of the current invention as claimed, especially in regards to "effective administration"of prosaposin, and for overcoming the intrinsic unpredictability of this art; and in regards to model systems not described in the instant application that do not address the issues encompassed by the full breath of the claims. Thus, it remains unknown how to carry out the claimed invention without undue experimentation to determine such, for the reasons made of record.

It is noted that the Declaration states that the 14-mer sequence derived from saposin C also crosses the blood brain barrier, as the specification had shown for the iodinated 18-mer species; thereby enabling use of this saposin C-fragment across the BBB (i.e., in regards to *pp* 14).

9. Claims 12-25 are again rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the reasons made of record, and as follows.

Applicants argue throughout the response (e.g., on pages 4, 6 & 7) that "a person of ordinary skill in the art can effectively practice the method of the invention", based on the references and experiments discussed in the Declaration. This is not persuasive for the reasons stated above in the discussion of the Declaration.

Applicants argue on page 5 of the response that "the PTO then focuses on the blood brain barrier issue", and that "[t]he PTO's skepticism regarding the ability of the subject neurotrophic factors to selectively target responsive cells with high enough local concentration thereof is unfounded". Although the BBB issue was raised in the previous Office action concerning "effective administration", this is but one of a number of problems associated with "effectively" treating any neurodegenerative disease or demyelinating disorder, as already made of record. Further, in regards to Applicants' comments that topically and intracerebrally or direct injection into the cerebral spinal fluid are possible, Hefti teaches that intracerebral administration of neurotrophic factors is "inadequate for human use" (i.e., not enabled; pg. 689, 1st column). Moreover, topical administration has the same problems of overcoming a hydrophobic barrier, similar to that of the BBB.

Applicants argue on page 6 of the response that the Barinage article supports the contention that *in vitro* work on IGF-1, BDNF and CNTF forms the basis for pharmaceutical companies to initiate clinical studies. However, there is no comment in Barinage that this was the sole reason for "initiating clinical studies". Moreover, no guidance is provided in the specification on how to "initiate clinical studies". In contrast, Barinage points that the clinical trial on CNTF was "unblinded", and that the "company has tried to salvage the trial by applying to the Food and Drug Administration to continue it with lower doses aimed at reducing the side effects" (pg. 773, 2nd *pp*). In other words, *in vitro* neurotrophic activity does not "correlate" with *in vivo* efficacy, as asserted by the Applicant.

Applicants argue on page 7 of the response that "[r]egardless of the problems discussed in the art in treating neural degeneration, promoting neural protection and increasing myelination, it has clearly been shown that prosaposin and neurotrophic fragments derived therefrom can successfully accomplish these". However, no documentary evidence is provided to support Applicants' conclusion; especially in regards to where such basis is found in the specification. Without proper neural structure (i.e., that is destroyed following damage or injury or disease), no proper function is expected, until functional synaptogenesis is restored; and then only if the neuron or oligodendrocyte (in the central nervous system) or Schwann cell (in the peripheral nervous system) does not die. The Applicant comments that "[t]hese experiments were performed using similar parameters as those described (i.e., proteins/peptides, dosages, delivery methods, types of neural disorders). This post-filing date data is relevant because similar methods were used therin as were discussed in the specification." In contrast, the Examiner's extensive comments made above in relation to each of the exhibits presented in the Declaration clearly contradict this assertion. Thus, the specification was not enabling "as of its filing date". The Applicant then comments on page 9 of the response that "[t]o determine whether a specification is enabling, the factors to be considered are summarized in *Ex parte Forman* and *In re Wands*." The Examiner agrees. In fact, the previous Office action discussed in detail why the limited disclosure in the specification was not enabling for the claimed neurological diseases and the very broad scope for efficacy and administration of the claimed prosaposin or neurotrophic fragments to a mammal (i.e., as it also encompasses the *in vivo* neural tissue of claim 18). In brief,

(1) treatment of neurological disease states is an unpredictable art (i.e., including neural degeneration and demyelination),

(2) "preventing", "slowing", or "effectively treating" neurological damage (i.e., the result of a demyelinating disorder or neuronal degeneration) often results in neuronal cell death (see Liebermann; see also pg. 1354, *pp*6, of the Merck Manual, as it relates to the demyelinating disorder, MS); therefore, treatment of neurological degeneration is not predictable because damaged neurons die, and "prevention" means no cell death.

(3) neurons do not regenerate in the CNS (e.g., see Jackowski, pg. 305, last *pp*); therefore, treatment of neuronal degeneration is not predictive because regeneration is required to effectively treat degeneration, and the associated demyelination (i.e., including oligodendrocytes that are replaced by astrocytic scar tissue; see Merck manual, pg.1354),

(4) without re-establishment of synaptogenesis, there is no functional neuronal regeneration (e.g., see Liebermann or Jackowski); and therefore no "prevention", "slowing" or "effective treatment" of neuronal cell death,

(5) efficacy and effective administration of compounds, such as prosaposin, that do not readily cross the blood brain barrier (BBB), for example, require guidance as to route of administration, duration of treatment and what constitutes an effective dose in order to practice the proposed invention *in vivo*, which are absent in the instant specification.

Taking this one step further, to practice the proposed invention, sufficient guidance would be needed by a routine practitioner to administer any prosaposin-derived molecule to the CNS, because the mode of action of these proteins is unknown and can not be extrapolated to what constitutes an "effective" dose *in vivo*, for example, based solely on a prophetic 10,000-fold range of dosages the Applicants refers to on page 4 of the response. The instant specification has also failed to disclose how these parameters are to be determined, how a similar method as disclosed in the instant specification was practiced in the art with a different agent, or to provide even a single working *in vivo* example of the claimed method. In the absence of this guidance a practitioner would have to resort to a substantial amount of undue experimentation involving the variation in the amount and duration of administration of the prosaposin-derived compounds of the instant invention and in determining a suitable route of administration. The instant situation is directly analogous to that which was addressed *In re Colianni*, 195 USPQ. 150, CAFC, which held that a "[d]isclosure that calls for application of "sufficient" ultrasonic energy to practice claimed method of fusing bones but does not disclose what "sufficient" dosage of ultrasonic energy might be or how those skilled in the art might select appropriate intensity, frequency, and duration, and contains no specific examples or embodiment by way of illustration of how claimed method is to be practiced does not meet requirements of 35 U.S.C. 112 first paragraph". Therefore, it would not be expected that the skilled artisan could even begin to successfully use the instant invention as disclosed for the reasons stated above, and because the instant specification discloses no assay for determining when, or if, the Applicants' invention works *in vivo*.

Applicant argues on page 8 of the response that the instant claims are directed to "preventing or slowing and treating" the various neurological disorders of the nervous system (i.e., as it relates to claims 14 & 25), "not to curing the listed disorders". Applicants then allude to subsequent studies, which supposedly are reflected in the submitted Declaration. However, the issue is that there is no method steps on how to effectively treat any specific disease state within the specification, nor assays provided by which the skilled artisan would know when these disease states were "prevented", "slowed" or "treated" and, as such, merely constitutes an invitation to experiment.

In summary, the Examiner's position is that Applicants have given no guidance nor any solutions nor any examples on how to overcome any of the problems associated with preventing diseased neurons from degenerating, demyelinating or dying; nor how to "effectively administer" especially the prosaposin protein into the CNS *in vivo*; nor how any of the unique disorders recited in the claims, each with their unique etiology, can be effectively treated, especially within the CNS; nor how to assay when or if the instant invention works *in vivo,* nor what parameters could be assayed to determine when the proposed invention would effectively treat any of the claimed disorders in this very unpredictable art; nor how one can extrapolate such from that disclosed within the specification. The specification discloses only three *in vitro* tissue culture studies using NS20Y neuroblastoma cells and one *ex vivo* study culturing newborn mouse cerebellar explants with saposin C and with 18-mer and 22-mer fragments of saposin C in which outgrowth of myelinated neurons increased 2-fold over control cultures. Therefore, there is no

expectation of success, nor "large body of evidence", that the skilled artisan can carry out the instant invention to treat, prevent or slow any neurological/ demyelinating disorder or disease, as claimed, without undue experimentation to determine such; especially as it relates to the unpredictable and uncharacterized disease states recited in claims 14 & 25. Thus, a *prima facie* case of nonenablement has clearly been established, as set forth in *Ex parte Forman* and *In re Wands*. The claims merely constitute an invitation to experiment, and as such, are not enabled.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donald Adams, can be reached on (703) 308-0570. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert C. Hayes, Ph.D.
February 25, 1997

MARIANNE P. ALLEN
PRIMARY EXAMINER
GROUP 1800